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INTERMEDIATE

CASE REPORT: CLINICAL CASE

All-*trans* Retinoic Acid–Induced Isolated Myocarditis

A Case Report and Review of the Literature

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ABSTRACT

All-*trans* retinoic acid (ATRA) is the mainstay of treatment in patients with acute promyelocytic leukemia. Despite being effective, it can lead to cardiac complications either as a component of ATRA syndrome or an isolated form denominated as ATRA-induced isolated perimyocarditis. We present a case of this complication and review the literature. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:2101–6)

A 23-year-old woman diagnosed with acute promyelocytic leukemia (APL) was admitted to the hematology unit. Induction therapy consisting of idarubicin 20 mg/day (on the second, fourth, sixth, and eighth days) and all-*trans* retinoic acid (ATRA) at a dose of 45 mg/m^2/day was initiated. The patient had been well until 18th day from the initiation of therapy. However, she experienced a typical chest pain in the left-retrosternal region without radiating; thus, she was referred to the cardiology clinic for evaluation of chest pain on the 18th day of induction therapy. Her temperature was 36.8°C, blood pressure was 120/70 mm Hg, the heart rate was 86 beats/min, respiratory rate was 12 breaths/min, and the oxygen saturation was 98%. The patient looked anxious.

LEARNING OBJECTIVES

- To recognize ATRA-related cardiac complications.
- To understand the clinical course of ATRA-induced perimyocarditis.
- To take action against this complication.

MEDICAL HISTORY

The patient had no medical history or family history of cardiovascular diseases or risk factors. She did not report history of smoking, medication, or drug abuse. Findings on a screening electrocardiogram were normal (Figure 1A). Transthoracic echocardiography (TTE) before the induction therapy revealed no wall motion abnormality and a normal left ventricle ejection fraction (LVEF).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for chest pain in this patient included acute coronary syndrome, viral

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ABBREVIATIONS AND ACRONYMS

APL = acute promyelocytic leukemia

ATRA = all-*trans* retinoic acid

CRP = C-reactive protein

CT = computed tomography

LVEF = left ventricle ejection fraction

MRI = magnetic resonance imaging

TTE = transthoracic echocardiography

myocarditis and/or pericarditis, stress cardiomyopathy, and endocarditis.

INVESTIGATIONS

Electrocardiography revealed ST-segment elevation, mainly in the anterior and lateral derivations (**Figure 1B**). TTE revealed globally reduced LV systolic function with an EF of 43% (Videos 1, 2, and 3). Speckle tracking echocardiography in the apical 3-chamber view also showed reduced global longitudinal myocardial deformation of -14.0% (Video 4). Laboratory test findings indicated a white blood cell count of 3.9 $\times$ 10^3/μl, troponin I of 2,341.6 ng/l (range: 14 to 42.9 ng/l), C-reactive protein (CRP) of 22.2 mg/dl (range: 0 to 0.8 mg/dl), and procalcitonin of 0.21 ng/ml (range: 0 to 0.14 ng/ml). There were no signs or symptoms suggestive of infection. Coronary computed tomography (CT) was performed promptly and revealed that there was no obstructive lesion in a given coronary artery (**Figure 2**). In the view of the possibility of ATRA-related toxicity, we ceased to give the ATRA as the troponin level peaked (6,936.3 ng/l) on the 21st day of treatment. Three days later, we reinitiated the drug as troponin values started to decrease below 400 ng/l. Nonetheless, because chest pain was exacerbated and troponin (5,911 ng/l) and CRP (29.4 mg/dl) levels peaked again, the drug was discontinued, and cardiac magnetic resonance imaging (MRI) was performed on the same day. T1 (**Figure 3A**) and T2 (**Figure 3B**) mapping showed prolongation in relaxation time in the basal inferolateral region and all segments in the septum, consistent with interstitial edema. In addition, the post-gadolinium T1 mapping showed late enhancement in the inferolateral wall with an extracellular volume fraction of 59% (**Figure 3C**). LVEF determined by cardiac MRI was 45% and similar to that measured by TTE.

MANAGEMENT

A beta-blocker and angiotensin-converting enzyme inhibitor were initiated as soon as systolic dysfunction was detected. Because of low platelet count (20,000 $\times$ 10^3/μl), neither an antiplatelet nor an anticoagulant agent could be given. No additional medical treatment was given.

DISCUSSION

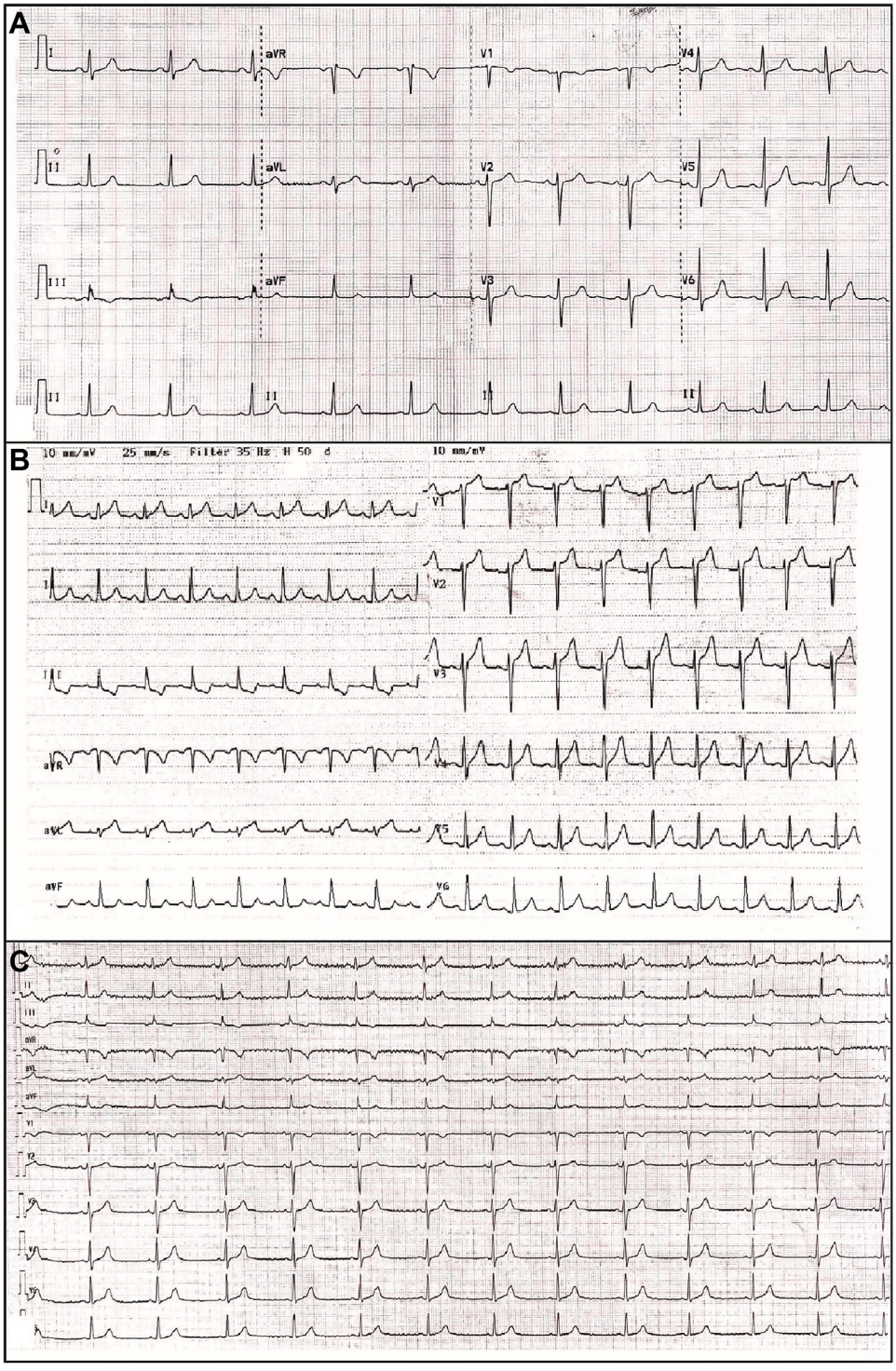
ATRA syndrome is characterized by fever, hypotension, pulmonary infiltration, and pericardial effusion; it is seen in one-fourth of the patients receiving ATRA. Cardiac involvement can be seen both as a component of ATRA syndrome and as an isolated perimyocarditis. The clinical picture may resemble acute coronary syndrome and viral myocarditis. It can be difficult to ascertain whether the perimyocarditis is a component of the ATRA syndrome or is a purely drug-related toxic phenomenon. However, it occurs, the pathological mechanism is thought to be caused by ATRA-induced promyelocyte maturation, cytokine release causing increased capillary permeability and endothelial damage, and subsequent extravasation and tissue infiltration of APL cells (1). In our case, the patient did not express other findings suggestive of ATRA syndrome, such as fever, hypotension, respiratory distress, and weight gain due to generalized edema and pleural effusion. Although increase in troponin level, typical chest pain, and changes in electrocardiography and echocardiography findings suggested acute coronary syndrome, the patient's characteristics and the absence of cardiovascular risk factors raised the suspicion of a drug-related complication. Hence, we performed coronary CT to exclude coronary artery occlusion. Mitigating symptoms with the cessation of the drug and peaking troponin levels after re-initiation of the drug indicated that this clinical picture was ATRA-induced perimyocarditis (**Figure 4A**). Concomitant increase in CRP (**Figure 4B**) and procalcitonin levels also suggested the inflammatory nature of the underlying event. Eventually, the diagnosis was confirmed with cardiac MRI findings.

Thus far, there are limited numbers of studies reporting the cases of ATRA-induced isolated perimyocarditis in the literature (**Table 1**). In these cases, almost all patients were young (9 to 58 years) and experienced the disease within 3 weeks following the initiation of the induction therapy. Our patient's age (23 years) and the emergence of the disease (18th day) are consistent with the previous cases. Different electrocardiographic changes and different myocardial segment involvements on echocardiography reported in the literature indicate that ATRA does not exhibit a specific involvement pattern. We did not consider anti-inflammatory therapy. In many of the previous case reports, nevertheless, anti-inflammatory therapy such as dexamethasone and prednisone, along with conventional heart failure therapy, was initiated to alleviate myocardial and pericardial inflammation.

FOLLOW-UP

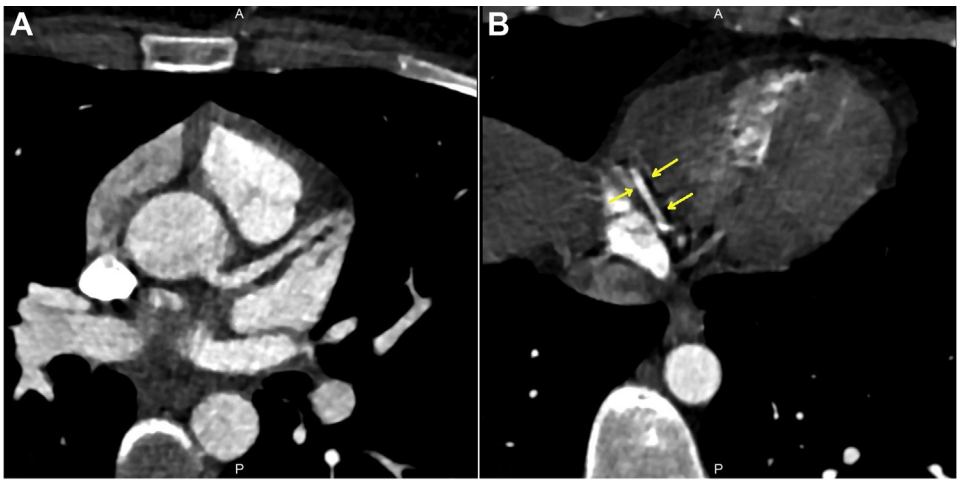
The patient was completely asymptomatic and the troponin level (4.2 ng/l) was within normal limits

FIGURE 1 The Electrocardiographic Records of the Patient



(A) Baseline electrocardiography before all-*trans* retinoic acid treatment. **(B)** Electrocardiography shows ST-segment elevation, mainly in the anterior and lateral derivations during chest pain. **(C)** Electrocardiography shows resolution of ST-segment elevation after the discontinuation of all-*trans* retinoic acid.

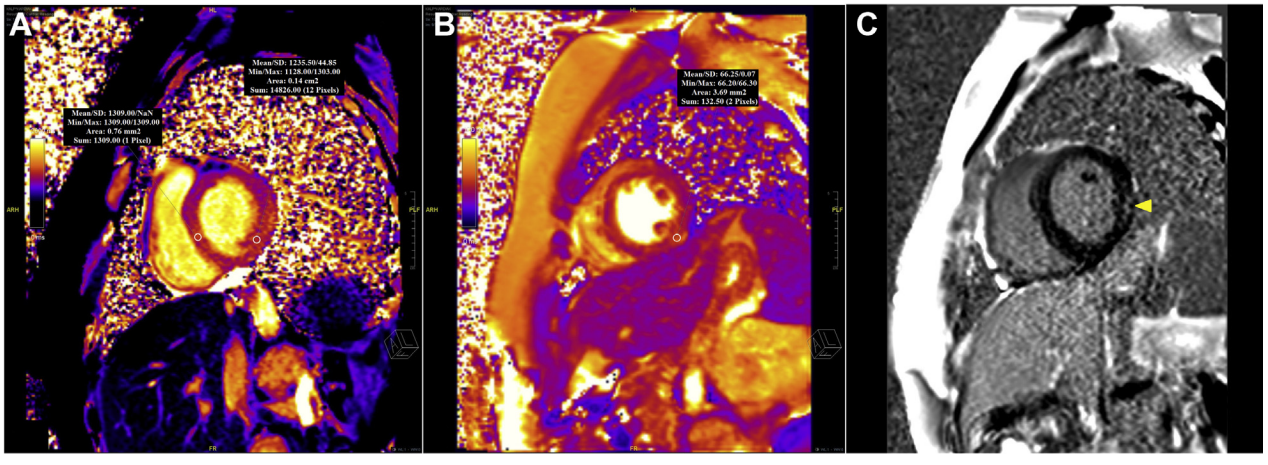
FIGURE 2 The Cardiac Computed Tomography of the Patient



Cardiac computed tomography reveals no coronary obstructive lesion in the **(A)** left and **(B)** right system. **Arrows** indicate the crux segment of the right coronary artery.

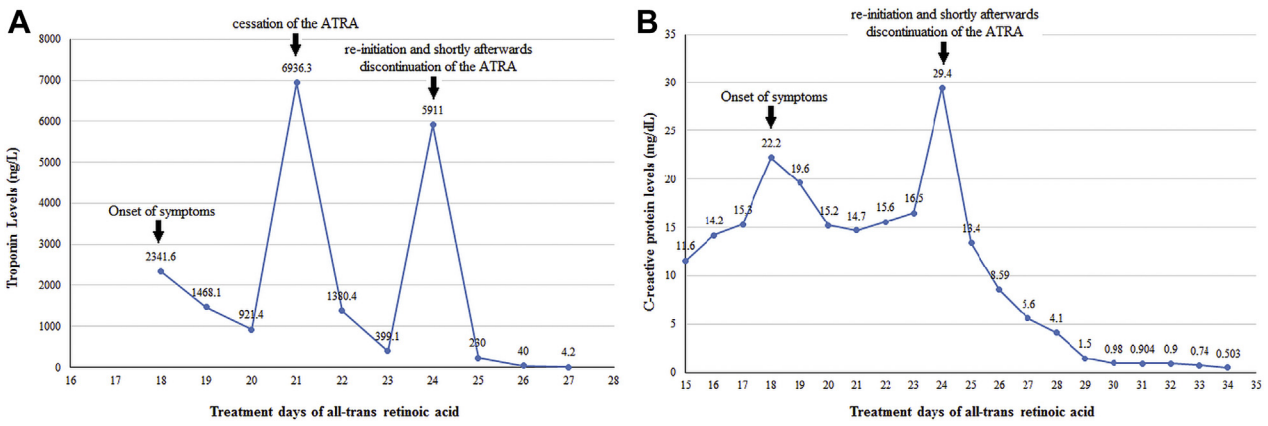
3 days after the discontinuation. CRP (0.503 mg/dl) and procalcitonin (0.016 ng/ml) also returned to their normal levels 10 days after the discontinuation. Electrocardiogram showed resolution of ST-segment elevation (**Figure 1C**). TTE revealed normal LV systolic function with an EF of 56% (Videos 5, 6, and 7). Speckle tracking echocardiography in the apical 3-chamber view indicated normal global longitudinal myocardial deformation of -27.7% (Video 8). Arsenic trioxide has been initiated for leukemia treatment.

FIGURE 3 Cardiac Magnetic Resonance Imaging Findings of the Patient



Cardiac magnetic resonance imaging reveals prolonged native myocardial relaxation times in T1-weighted mapping. A region of interest placed in the septum and the inferolateral wall shows an increase in T1 relaxation times. **(A)** T1 signal is 1,309 ms for the septum and 1,235 ms for the inferolateral wall, consistent with interstitial edema. (For normal myocardium, the mean/2SD value is 950/42 ms). **(B)** In the T2 mapping, the area of interstitial edema in the inferior wall has an increased relaxation time of 66 ms (for normal myocardium, mean/2 standard deviations is 50/4 ms). **(C)** The post-gadolinium T1 mapping shows late enhancement in the inferolateral wall **(yellow arrowhead)** with an extracellular volume fraction of 59%. max = maximum; min = minimum; SD = standard deviation.

FIGURE 4 The laboratory Findings of the Patient



Graph of **(A)** troponin I and **(B)** C-reactive protein levels according to treatment days of the ATRA. ATRA = all-*trans* retinoic acid.

CONCLUSIONS

ATRA-induced isolated perimyocarditis should be kept in mind in patients with APL. Although rare, it warrants high suspicion and early detection because it can cause devastating complications. In the present case, we demonstrated the ATRA-induced isolated perimyocarditis by using a variety of imaging modalities including 2- and 3-dimensional echocardiography, coronary CT, and cardiac MRI. In our case, the complete recovery of myocardial function was achieved by discontinuation of ATRA and conventional heart failure therapy.

AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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TABLE 1 All-*trans* Retinoic Acid–Induced Isolated Perimyocarditis Cases in the Literature

First Author (Ref. #)	Year	Age (yrs), Sex	Day of Occurrence*	Ejection Fraction, %	Wall Motion Abnormalities	Treatment	Changes on Electrocardiography
Choi et al. (2)	2011	39, female	18	38	Basal and midanterior	Dexamethasone and diuretic	No change
Ben El Makki et al. (3)	2019	27, male	10	33	Diffuse	Vasopressors, diuretic, ACE inhibitor, beta blocker	Diffuse ST-segment elevation
Klein et al. (4)	2007	34, female	19	No data	No data	No specific treatment	Diffuse ST-segment elevation
Klein et al. (4)	2007	46, male	23	No data	Diffuse	No specific treatment	Diffuse ST-segment elevation
Fabbiano et al. (5)	2005	45, male	23	No data	Posterolateral	No specific treatment	Lateral ST-segment elevation V_1 to V_2 ST-segment depression
Van Rijssel et al. (6)	2010	58, male	21	No data	No data	The patient died 2 days later	No data
Carcelero et al. (7)	2018	35, male	16	35	Diffuse	Anti-inflammatory agents, diuretics, ACE inhibitor, and dobutamine	Diffuse ST-segment elevation
Isik et al. (8)	2010	9, female	Within first week	40	Diffuse	Prednisolone, inotropics, and diuretics	Diffuse voltage depression

*Day of occurrence indicates how many days the event occurred after induction therapy.
ACE = angiotensin-converting enzyme.

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KEY WORDS drug toxicity, imaging, myocarditis

APPENDIX For supplemental videos, please see the online version of this paper.